4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-N-0236]

Prioritizing the Addition of Maximum Daily Exposure Information and Removing Dosage Form Information From the Inactive Ingredient Database; Establishment of a Public Docket; Request for Comments

AGENCY: Food and Drug Administration, Department of Health and Human Services (HHS).

ACTION: Notice; establishment of a public docket; request for comments.

SUMMARY: The Food and Drug Administration (FDA, we, or Agency) is announcing the establishment of a docket to solicit comments that will assist the Agency in determining how best to prioritize the addition of maximum daily exposure (MDE) information for inactive ingredients that do not currently include MDE information in the Center for Drug Evaluation and Research's Inactive Ingredient Database (IID) and whether to restructure the IID by removing dosage form information.

DATES: Submit either electronic or written comments on the notice by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2022-N-0236 for "Prioritizing the Addition of Maximum Daily Exposure Information and Removing Dosage Form Information From the Inactive Ingredient Database; Establishment of a Public Docket; Request for Comments." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential

Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Susan Zuk, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 6684, Silver Spring, MD 20993-0002, 240-402-9133, Susan.Zuk@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

The IID provides information on inactive ingredients in FDA-approved drug products.[1] An inactive ingredient, or excipient, is any component of a drug product other than an active ingredient (21 CFR 210.3(b)(8) and 314.3(b)). Generally, the IID identifies excipients that appear in approved drug products for a particular dosage form and route of administration. This information in the IID has been used by all segments of industry as an aid in developing new drug products, including new generic drug products. For example, excipients used in drug products submitted in an abbreviated new drug application are required to be safe at the levels proposed and under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug (see sections 505(j)(4)(H)(i) and (ii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(4)(H)(i) and (ii))). The IID provides evidence that a particular excipient was previously permitted by FDA in specific levels, routes of administration, and dosage forms in FDA-approved products. FDA may consult the IID when performing regulatory filing reviews and technical reviews of applications as part of an evaluation of whether the proposed levels of excipients in drug product formulations are acceptable or require additional documentation to support their use.

FDA made certain enhancements to the IID in 2020 consistent with the Generic Drug User Fee Amendments (GDUFA) Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II commitment letter).[2] One of these enhancements permits users to perform electronic queries to obtain accurate maximum daily intake (MDI) and MDE information for each route of administration for which data are available. MDE is defined as the total amount of the excipient that would be taken in a day based on the

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[1] For more information on the IID, see the draft guidance for industry entitled "Using the Inactive Ingredient Database" (July 2019). When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[2] See the GDUFA II commitment letter, p.17, at https://www.fda.gov/media/101052/download.

maximum daily dose of the drug products in which it is used. MDE can also be referred to as MDI for oral drug products. FDA has steadily increased the number of excipient records that display MDE with each publication of the IID,[3] but not all excipients in the IID have MDE information. The inclusion of such information could enhance the ability of applicants to reference IID information in support of proposed levels of excipients in their drug products. In meetings with FDA, stakeholders have asked about FDA's plan to prioritize the addition of MDE information and have suggested that FDA focus on specific excipients that the stakeholders consider to be of high priority.

Further, some stakeholders have expressed that the numerous records in the IID for each excipient can be confusing. Each IID record includes the excipient, its route of administration, and its dosage form. An excipient search can yield a lengthy list of dosage forms for each route of administration, which could make finding the most appropriate IID record to reference challenging. Some stakeholders have suggested that FDA could remove dosage form information from the IID to simplify searches. We believe such an approach would be consistent with the GDUFA II commitment letter, which describes upgrades to the IID to provide excipient MDE information associated with particular routes of administration. However, we recognize that some stakeholders may find the IID's dosage form information helpful for drug product development. For example, applicants may refer to this information to confirm that FDA has approved drug products in certain dosage forms that contain an excipient at a particular level. For these applicants, removal of dosage form information from the IID could hinder their drug development program.

II. Other Issues for Consideration

FDA is considering how best to prioritize the addition of MDE information and plans to target those excipients deemed to be high priority by various stakeholders. Under such a plan, individual excipients could be designated for prioritization from those currently listed in the IID

[3] The IID is updated on a quarterly basis at https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

without MDE information. Alternatively, priority excipients could be designated based on a category of drug products in which they are used (e.g., excipients used in oral or topical products), and then FDA would prioritize adding MDE information for those excipients included in that category of drug products. FDA intends to develop a priority list based on feedback to this *Federal Register* notice. FDA will consider those excipients that are a high priority for multiple stakeholders and will also consider stakeholders' rationale for inclusion of specific excipients in developing the priority list. FDA is also considering how to post information about recent updates to the IID based on efforts related to this *Federal Register* notice.

FDA intends also to explore the feasibility of modifying the IID structure to eliminate dosage form information if feedback to this *Federal Register* notice indicates that such action would benefit drug developers and other stakeholders.

Interested persons are invited to provide detailed comments on all aspects described in this notice. To facilitate this input, FDA has developed the following list of questions. These questions are not meant to be exhaustive, and FDA is also interested in other pertinent information stakeholders would like to share on this topic. In all cases, FDA encourages stakeholders to provide the specific rationale and basis for their comments, including available supporting information.

1. Should FDA focus on adding MDE information for certain excipients? If so, which excipients should be prioritized for inclusion of MDE information and why?

2. Should FDA focus on prioritizing excipients used in certain categories of drug products (e.g., oral or topical products)? If so, which categories and which specific excipients used in those categories should be prioritized and why?

3. Is dosage form information in the IID helpful to your drug development program? If so, please explain how dosage form information in the IID is used in your drug development program.

4. Is the current structure or format of the IID difficult to navigate? If so, how can it be improved?

Dated: March 15, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022-06031 Filed: 3/21/2022 8:45 am; Publication Date: 3/22/2022]